Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 62, No. 18, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.06.010

EDITORIAL COMMENT

Mental Stress and Cardiac Troponin

Keep Calm and Carry On?*

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Cardiac troponin (cTnT) has served us well for more than a decade as the biochemical benchmark for the diagnosis of myocardial infarction. During the past years, it has become clear that cTn elevation also may be seen in many other conditions affecting cardiomyocyte integrity (e.g., congestive heart failure, stable coronary artery disease, or atrial fibrillation) (1,2). Research on this area has been fueled following the implementation of high-sensitivity assays that made it possible to detect circulating cTn levels in community-dwelling populations. Even in these individuals, cTn reflects the presence of chronic cardiac abnormalities and is highly predictive for adverse outcome, namely mortality and heart failure admissions (3,4).

See page 1694

In this issue of the *Journal*, Lazzarino et al. (5) present interesting new data on the implications of cTn in community dwellers. The authors measured cTnT (cTnT) using a high-sensitivity assay in 508 men and women without cardiovascular disease. Measurements were performed 75 minutes after a mental stress test. The authors found a positive association between the stress level (expressed as the salivary cortisol increase) and detectable cTnT levels (n = 85 [16.7%]). This association was significant in multivariable analyses, consistent following quite extensive adjustment, and seen both in individuals with and without coronary artery calcification defined by the Agatston score.

These findings are novel in nature and intriguing at the same time. As always with cross-sectional studies, the word caution is needed when interpreting the data because it is difficult to determine the causal sequence between mental stress and detectable cTnT levels. Lazzarino et al. (5) list a multitude of possible pathways and mechanisms, some of which are given below.

1. There could be a direct impact of cortisol on cardiomyocytes through increased oxidative stress, modulation of ion channels, or potentiation of adrenergic signaling. However, the baseline salivary cortisol level before mental stress exposure was not associated with detectable cTnT levels, which argues against this hypothesis.
2. The authors discussed moreover whether cTnT leakage could have been caused by clinically silent myocardial necrosis due to the rupture of noncalcified coronary plaques that remained undetected by the means of cardiac computed tomography (CT). Although interesting, this hypothesis is highly speculative and needs to be investigated by other means, preferably coronary imaging.
3. Mental stress might have caused cTnT leakage directly via increased sympathomimetic activity, as seen in Takotsubo cardiomyopathy. Intriguingly, previous studies seem to support this hypothesis because left ventricular wall motion abnormalities and regional perfusion changes have been noted in patients with coronary artery disease subjected to mental stress (6). If this translates also to cTn increases, there would be major consequences on how we measure and interpret cTn levels in clinical situations. Just think of cTn measurement under potentially stressful conditions such as in chest pain patients admitted to a busy emergency department.

   This leads directly to the question whether higher cTn levels after mental stress would reflect a physiological response similarly to cTn increases seen after physical exercise (7). In other, more provocative terms: will even ordinary people (or their doctors) increase in their cTn levels when subjected to daily hassles in life (e.g., traffic congestion; arguing with teenagers [6]; working on-call duty; reading new guidelines on the definition of myocardial infarction), and what importance would this have? Unfortunately, due to its design, the study from Lazzarino et al. (5) does not help us with this question: cTnT was not measured at baseline (i.e., before mental stress exposure) why it was not possible to definitely determine whether mental stress was the cause of cTnT increase.
4. However, even the opposite could be true. Hyperresponsiveness to mental stress might identify a phenotype that is more prone to develop subclinical cardiovascular disease, which in turn is reflected by persistently detectable cTnT levels. Of all discussed hypotheses explaining the findings in the present study, this appears to be the most plausible one, as acknowledged by Lazzarino et al. (5), who, however, are surprisingly vague about clinical implications.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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Cardiovascular hyperresponsiveness to mental and emotional stressors has long been regarded to be a potential contributor to the individual differences in cardiovascular disease risk. Heightened cardiovascular stress reactivity, primarily the increase in heart rate and blood pressure, results in increased oxidation of low-density lipoproteins and higher serum concentrations of both proinflammatory cytokines and blood insulin, and portends to the development of structural and functional cardiovascular abnormalities. A large body of evidence links cardiovascular hyperresponsiveness to objective outcomes including hypertension, atherosclerosis, left ventricular hypertrophy, and cardiovascular disease mortality. Comprehensive reviews on this topic are available (6,8).

Mental stress appears thus to provide a milieu of increased vulnerability to the heart and the vessels. This is acknowledged in current guidelines recommending diverse stress intervention programs (e.g., cognitive behavioral interventions, relaxation training, or regular physical exercise) (9). The question, however, is for how long or how aversive a stressor has to be to lead to impaired cardiac functioning? The study from Lazzarino et al. (5) provides new evidence in this regard as it clearly demonstrated that even shorter episodes of obviously benign stress are associated with detectable cTnT levels which if persistently raised, need to be regarded as an indicator of adverse processes affecting the heart.

The study from Lazzarino et al. (5) is also important because it emphasizes the notion that cTn not only reflects prevalent cardiac abnormalities but also a risk pattern portending to their development. cTn has, for example, been shown to be associated with hypertension, smoking, obesity, hyperlipidemia, diabetes, and lower levels of physical exercise (3,4,10,11). The study from Lazzarino et al. (5) adds short episodes of mental stress to this list. Further studies are now warranted to investigate whether chronic stressors (e.g., low social support, job stress and exhaustion, racial discrimination) would also result in similar findings.

What shall we do about this? Shall we simply recommend our patients to try not to get stressed? Unfortunately, life is more complicated than this and all of us will have to cope with different degrees of stress exposure even in the future. Still, it is difficult to determine at which level mental stress turns from healthy to adverse. Nevertheless, we can help our patients to cope with negative stress-related effects by referring them to psychosocial intervention programs - an important but likely underused treatment option (12).

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Key Words: atherosclerotic plaque ▪ computed tomography ▪ myocardial infarction ▪ psychological stress ▪ troponin T.